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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/830,502	10/09/2001	Francis Barany	19603/2615	8225

7590 10/07/2004

Michael L Goldman
Nixon Peabody
Clinton Square P O Box 31051
Rochester, NY 14603

EXAMINER

HUTSON, RICHARD G

ART UNIT PAPER NUMBER

1652

DATE MAILED: 10/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/830,502

Applicant(s)

BARANY ET AL.

Examiner

Richard G. Hutson

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 06 May 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 9 and 48-50 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 9 is/are allowed.
- 6) ☒ Claim(s) 48 and 49 is/are rejected.
- 7) ☒ Claim(s) 50 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>5/2004</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicants cancellation of claims 1-8, 10-47, amendment of claim 9 and the addition of new claims 48-50, in the paper of 5/6/2004, is acknowledged.

Claims 9, and 48-50 are still at issue and are present for examination.

Applicants' arguments filed on 5/6/2004, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

It is noted that applicants response, while stating that it is for application serial number 09/830,502, contains at the top of pages 2-25 of the response "Serial No. 10/197,280". It is unclear what the relationship of this referred to serial application number is or if this was merely a typographical error.

Information Disclosure Statement

Applicants filing of the information disclosure statement filed on 5/6/2004, is acknowledged. Those references considered have been initialed.

Specification

The disclosure is objected to because of the following informalities:

The amendment filed 5/6/2004 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention.

The added material which is not supported by the original disclosure is as

follows: The amino acid sequences corresponding to SEQ ID NOs: 25-31 are considered new matter..

Applicant is required to cancel the new matter in the reply to this Office Action.

Appropriate correction is required.

Claim Objections

Claim 50 is objected to because of the following informalities:

Claim 50 is objected to because claim 50 (a thermostable ligase encoded by SEQ ID NO: 2) a duplicate of claim 9 (a thermostable ligase having the amino acid sequence of SEQ ID NO: 1).

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 49 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 49 is rejected because the recitation of SEQ ID NO: 32 is unclear as there does not appear to be a SEQ ID NO: 32 in the specification or sequence listing.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 48 and 49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection was stated in the previous office action as it applied to claims 1-8 and 10-15. In response to this rejection, applicants have cancelled claims 1-8 and added new claims 48-50.

Applicants do not specifically traverse the rejection as it may be applied to the newly added claims.

Claim 48 is directed to all possible thermostable ligases having a histidine adjacent to the KXDG motif replaced by an arginine.

As previously stated, the specification, however, only provides a few representative species encompassed by these claims. There is no disclosure of any particular structure to function/activity relationship in the disclosed species. The specification also fails to describe additional representative species of these enzymes by any identifying structural characteristics or properties other than the activities recited in claims 1, for which no predictability of structure is apparent. Further, applicants have only defined a single bacterium, *Thermus sp.* AK16D as a source of the claimed enzyme, while applicants claim all said enzymes having the recited functional limitation. Given this lack of additional representative

species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Claim 50 is rejected under this statute, because the newly added claims reference to SEQ ID NOs: 25-32 is considered new matter. Specifically it is the incorporation of SEQ ID NOs: 25-31(32) as discussed above under the objection to the specification.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claim 48 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for thermostable DNA ligases having the amino acid sequence of SEQ ID NO: 1, does not reasonably provide enablement for any thermostable ligase wherein a histidine adjacent to a KXDG motif is replaced with an arginine. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The rejection was stated in the previous office action as it applied to claims 1-8 and 10-15. In response to this rejection, applicants have cancelled claims 1-8 and added new claims 48-50.

Applicants do not specifically traverse the rejection as it may be applied to the newly added claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 48 is so broad as to encompass any thermostable ligase wherein a histidine adjacent to a KXDG motif is replaced with an arginine. The claim rejected under this section of U.S.C. 112, first paragraph places no structural limits on the claimed enzymes. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the thermostable DNA ligase from the *Thermus* sp. AK16D having the amino acid sequence of SEQ ID NO: 1.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as

encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any thermostable ligase with the claimed functional limitations, because the specification does not establish: (A) regions of the protein structure which may be modified without effecting the claimed ligase activity (i.e. fidelity); (B) the general tolerance of thermostable DNA ligases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue of a thermostable DNA ligase with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain the ligase activity claimed and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g., see Ngo et al. in *The Protein Folding Problem and Tertiary Structure Prediction*, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), it would require undue experimentation for one skilled in the art to arrive at the

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majority of those polypeptides of the claimed genus having the claimed ligase (i.e. fidelity) activity.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of amino acid modifications of any thermostable ligase. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of those thermostable ligases having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (703) 308-3804. The fax phone number for the organization where this application or proceeding is assigned is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

A handwritten signature in black ink, appearing to read 'Richard G. Hutson', with a stylized, cursive script.

Richard G Hutson, Ph.D.
Primary Examiner
Art Unit 1652

rg
9/29/2004